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Original Article

Improved air trapping evaluation in chest computed tomography in children with cystic fibrosis using real-time spirometric monitoring and biofeedback ☆

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Abstract

Background: The quality of chest Computed Tomography (CT) images in children is dependent upon a sufficient breath hold during CT scanning. This study evaluates the influence of spirometric breath hold monitoring with biofeedback software on inspiratory and expiratory chest CT lung density measures, and on trapped air (TA) scoring in children with cystic fibrosis (CF). This is important because TA is an important component of early and progressive CF lung disease.

Methods: A cross sectional comparison study was completed for chest CT imaging in two cohorts of CF children with comparable disease severity, using spirometric breath hold monitoring and biofeedback software (Copenhagen (COP)) or unmonitored breath hold manoeuvres (Gothenburg (GOT)). Inspiratory–expiratory lung density differences were calculated, and TA was scored to assess the difference between the two cohorts.

Results: Eighty-four chest CTs were evaluated. Mean (95%CI) change in inspiratory–expiratory lung density differences was 436 Hounsfield Units (HU) (408 to 464) in the COP cohort with spirometric breath hold monitoring versus 229 HU (188 to 269) in the GOT cohort with unmonitored breath hold manoeuvres ($p < 0.0001$). The Mean TA (95%CI) score was 6.93 (6.05 to 7.82) in COP patients and 3.81 (2.89 to 4.73) in GOT ($p < 0.0001$) patients.

Conclusions: In children with comparable CF lung disease, spirometric breath hold monitoring during examination yielded a large difference in lung volume between inhalation and exhalation, and allowed for a significantly greater measured change in lung density and TA score, compared to unmonitored breath hold maneuvers. This has implications to the clinical use of chest CT, especially in children with early CF lung disease.

Keywords: Cystic fibrosis; CF lung disease; Computer tomography; Image quality; Breath-hold monitoring; Trapped air

1. Introduction

Chest CT imaging of the lungs is an accepted and sensitive method to evaluate chronic lung disease in children with cystic fibrosis (CF) [1], Structural lung changes in CF are widely known to be closely related to infections with Gram-positive and Gram-negative bacteria [2–6], and to be unevenly distributed in the lungs [7,8]. Trapped air (TA) is an important

Abbreviations: CT, Computer tomography; TA, Trapped air; CF, Cystic fibrosis; HU, Hounsfield units; COP, Copenhagen; GOT, Gothenburg; FEV1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; BMI, Body mass index; SVC, Slow vital capacity; TLC, Total lung capacity; HU, Hounsfield unit; CFCT, Cystic fibrosis computer tomography; ICC, Intraclass correlation coefficient.

☆ The results of this study were presented by Thomas Kongstad in a workshop and a poster at the NACF Congress in Orlando, Florida, USA from 11-October-2012 to 13-October-2012.

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component of chronic airway diseases such as CF. It represents small airways involvement [9,10] and is best visualized on expiratory CT image sequences [11–13]. In recent years different methods of breath hold control have been described: conventional unmonitored breath hold with verbal instructions [3], spirometry triggered CT [14], spirometry monitored CT [15], controlled volume infant CT [6,16–19], and free breathing CT [20,21]. It has been previously reported that lung volume control during scanning improves the value of CT images in children with CF compared with healthy controls [9], but the impact on comparable groups of CF children has not been studied. We hypothesized that discrimination of disease severity from CT images would become more reliable when spirometric breath hold monitoring was used to guide the child during acquisitions of chest CT images. We tested this by comparing chest CT images acquired using "real-time" spirometric breath hold monitoring with biofeedback software to those acquired during unmonitored breath hold manoeuvres. Additionally, we were interested in assessing trapped air (TA) scoring obtained from chest CT scanning during monitored versus unmonitored breath hold manoeuvres.

2. Methods

2.1. Recruitment

Children with CF followed at the CF centre at Copenhagen University Hospital in Rigshospitalet (COP), Denmark, and the CF centre at Sahlgrenska Hospital in Gothenburg (GOT), Sweden, who were between 6 and 18 years of age were eligible for this study, if at least one chest CT examination for disease monitoring was available. A CF diagnosis was confirmed by sweat chloride test >60 mmol/l and/or genotyping for CF mutations.

Children followed at the CF centre in COP had chest CT imaging performed as part of a clinical prospective longitudinal CT study, that compared clinical parameters to the evolution of lung changes visualized on CT. All CT examinations were performed using spirometric monitoring. Full informed written consent was obtained from the parents or guardians of the children.

In GOT, routine CT examinations have been performed since 1997 [3] and CT images were selected from a group of CF children matched according to age, gender and lung function (FEV_1 and FVC, % predicted) at the day of CT scanning.

In order to achieve all possible matches of patient age and lung function between the two cohorts, two examinations from five individual GOT patients were allowed, since the examinations were at least 3 years apart.

2.2. Test procedures

Chest CT examinations were preceded by measurements of weight, height, lung function, and clinical evaluation. Body mass index (BMI) was calculated from the anthropometric data. At both centres CT scanning was performed in CF children who were clinically stable. In case of a pulmonary exacerbation, CT scanning was postponed at least 4 weeks.

2.3. Lung function

Spirometry (Jaeger Masterscreen PFT, CareFusion, Hoechberg, Germany) was performed on the day of the chest CT scanning utilizing ATS/ERS guidelines [22], and FEV_1 and FVC were recorded. The "all ages" reference equations were used to calculate the percent predicted values [23].

2.4. Chest CT acquisition at COP

All scans were done by volumetric spiral CT imaging on a Toshiba Aquillion 64 CT scanner (Toshiba Corporation, Tokyo, Japan), (100 kVp, mAs-modulation (SD = 19 in inspiratory and SD = 27 in expiratory sequences, rotation 0.4 s). The average total radiation dose for the inspiratory and expiratory CT scans was 1.41 mSv (range 0.78– 4.05). Images were reconstructed using a medium soft kernel (FC12) for 3 mm slices and a sharp kernel (FC52) for 1 mm CT slices. A full description of the scan protocol can be found online.

2.5. Real-time spirometric monitoring and biofeedback

Prior to chest CT scanning, an optimal supine slow vital capacity (SVC) measurement was obtained, and 10% and 90% of SVC values were calculated. An advanced breath hold technique was achieved by spirometric monitoring (JAEGER pneumotachograph connected to a portable computer) and biofeedback software, developed particularly for this purpose by the biomedical department and the authors (further description of software can be found online). The values from SVC were entered into the biofeedback software and displayed on a screen. Dynamic pulmonary volumes were displayed during breathing as a smiley-animation on a volume-time curve on the screen (Video still 1) (Fig. 1), to improve the incentive for the child to follow the instructions. Breath hold control was considered successful when the child reached the designated thresholds of below the 10% line

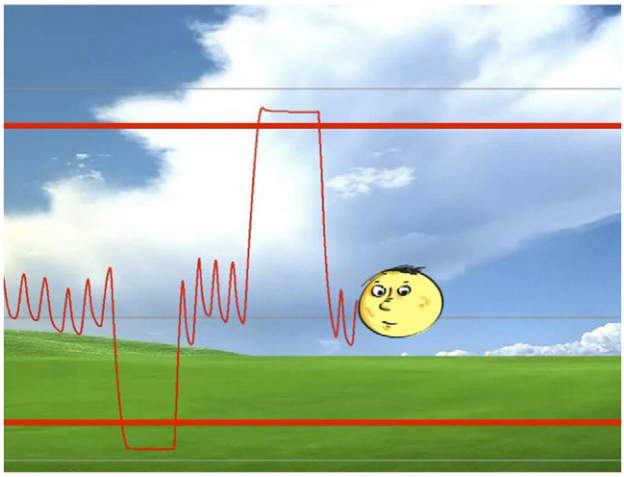

Fig. 1. Computer biofeedback displaying dynamic volume-time curve during scanning. The red lines mark the 10% and 90% of Slow Vital Capacity volumes to be reached for expiratory and inspiratory sequences. Refer to online supplement for a short video of the bio-feedback animation. Volume-time data are stored for documentation and post-processing.

(near expiratory reserve volume) and above the 90% line (approaching total lung capacity (TLC)) during expiratory and inspiratory manoeuvres.

During CT scanning, both the child and the instructor watched the animation on separate screens (Fig. 2). When breathing manoeuvres successfully reached corresponding thresholds with subsequent breath holds, image acquisition was initiated by a signal from the instructor to the technician (video recording of the procedure is available online).

2.6. Chest CT acquisition at GOT

The chest CT scanning protocol from Gothenburg has previously been reported [3]. From 2001 to 2010 a General Electric Light Speed Ultra CT scanner (GE Medical Systems, Milwaukee, WI, USA) was used at the GOT CF centre. (120 kVp, 120 mA, rotation 0.5 s). Since 2010 a General Electric Discovery 750 HD CT scanner was used. (GE Medical Systems, Milwaukee, WI, USA) (100 kVp, 50–100 mA (auto-mA noise index 30–30.37) rotation 0.4 s). Inspiratory CT images were obtained from the lung apex to base at 15 mm intervals using 1.25 mm slice thickness. For expiratory CT imaging, three 1.25 mm slices were obtained through the upper, middle and lower lung zones. Radiation dosage data was not saved for this study. Images were reconstructed using the standard GE bone algorithm. The breath hold was rehearsed prior to both sequences of the examination. Four slices were recorded for every inspiratory breath hold, with a total of 3 to 5 breath holds needed for the examination (dependent upon the size of the child). For expiratory scans 2 breath holds were needed. The child was trained to follow the pre-recorded automatic verbal instructions that were heard through the scanner loudspeaker. For inspiratory CT scans, the verbal instruction provided was: “Take a deep breath and hold!” For expiratory scans, the instruction was: “Take a deep breath, blow out all air and hold the breath there.” No particular breath hold criteria were evaluated [7,24].

2.7. CT image selection

At the GOT CF centre, limited slice expiratory chest CT images were acquired at 3 anatomical levels of the lungs (upper lung zone (2 cm above carina in 1–6 year olds and 3 cm above carina in 6–18 year olds), middle lung zone (at the level of carina) and lower lung zones (the slice closest to the middle between upper diaphragmatic level and level of carina)). For the lung tissue density measurements in this study, images were selected by the observer from the inspiratory sequences at the same anatomical levels.

Images from the COP group were similarly selected from both inspiratory and expiratory sequences, using the same anatomical levels. The different acquisition protocols used at the centres caused different noise/signal ratios on images. To avoid biased scoring and measurements, reconstruction slices of 3 mm from COP were selected and compared to 1.25 mm thin slices from GOT. These different slice thicknesses showed comparable noise/signal ratios and thus concealed the affiliation of the images. In order to conceal breath hold manoeuvre from the observers, patient and acquisition data were removed from images after applying a randomization number.

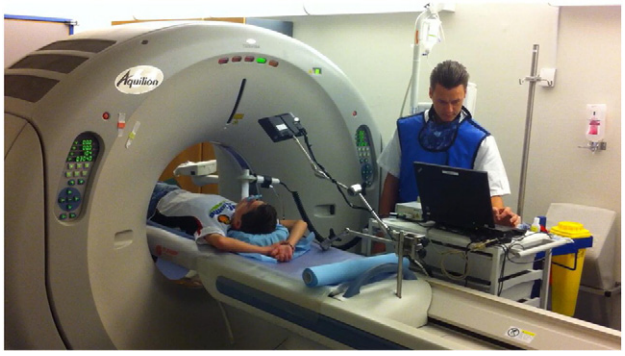

Fig. 2. The child is placed in the scanner with the monitor and the pneumotachograph held in place by a support arm.

2.8. Lung density measures

Lung tissue density on CT scans is measured in Hounsfield Units (HU). Lung density measurements were made using the circular region of interest selection tool, (Osirix software v. 4.1.1) at a window level of −500 HU, window width 1500 HU [25]. On the three expiratory images an area was selected, carefully avoiding trapped air, consolidation, cysts, bronchiectasis and large vessels (Fig. 3). The mean of the 3 expiratory values was calculated. Matched inspiratory images were evaluated in a similar manner, avoiding trapped air, consolidation, cysts, bronchiectasis, and large vessels. The difference between inspiratory and expiratory lung density was calculated (Δ-HU density) in order to correct for inter-scanner variability [26], and individual biological variation in lung density.

2.9. CT evaluation

Trapped air was scored by two trained observers (TK and TR), according to the limited slice method of Stick et al. [19], with a maximum score of 12 points if all 3 images showed TA > 50% of the lung area. A total score > 0 was defined as abnormal. Forty CTs selected randomly from the total patient population were scored by both observers, blinded to centre affiliation, and inter-observer agreement was determined. One observer (TK) scored the remainder of the subjects. To further compare the two cohorts, a CFCT score [27] was calculated by one observer (TK) after reviewing the whole lung inspiratory sequences. Trapped air (TA) score was excluded from the CFCT score since only 3 expiratory slices were acquired in the GOT CT examinations and thus the CFCT module was not applicable for TA scoring. The parameters scored were: bronchiectasis, bronchial wall thickening, mucous plugging, and parenchymal changes.

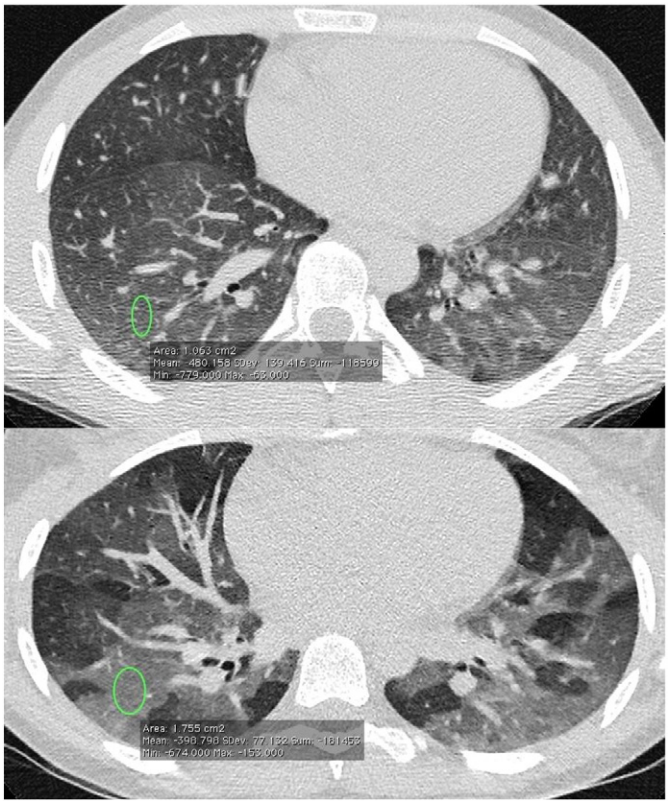

Fig. 3. Examples of expiratory images with Point Of Interest-markings of unaffected lung tissue without airtrapping, consolidation or large vessels. The mean value of attenuation inside the circle is registered.

2.10. Statistical analysis

Statistical analysis was performed using SAS v. 9.2. The unpaired t-test was used to compare patient characteristics, differences between inspiratory-expiratory lung density (Δ-HU density), and differences in CFCT score parameters. Spearman correlation coefficients were used to describe the correlation between TA score and Δ-HU density, as well as the correlation between 1 vs. 3 mm slice thickness densities. Intra-class correlation coefficient (ICC) [28] was used to assess agreement between the two observers for the total TA score, whereas a Kappa statistics was used to calculate agreement for the dichotomous TA outcomes. Comparison of TA scores between cohorts was done using Mann–Whitney non-parametric test. The influence of Δ-HU density on TA was examined by multiple regression analysis. P values <0.05 were considered to be statistically significant.

3. Results

Forty-two patients (22 males) from COP and 37 patients (21 males) from GOT were included in the study (age range 6–17 years). A total of 84 CT examinations were reviewed. Patient characteristics are presented in Table 1. There were no significant differences in age, gender, BMI or lung function obtained on the day of CT scanning.

3.1. Lung density

The mean lung density measurements (95%CI) for inspiratory and expiratory CT images from the COP cohort, which used spirometric monitoring and biofeedback (COP), were −875 HU (−882 to −869) and −439 HU (−466 to −410) respectively, with a mean Δ-HU density (95%CI) of 436 HU (408 to 464). In the GOT cohort that utilized unmonitored breath hold procedures, the corresponding inspiratory and expiratory lung density measurements were −834 HU (−845 to −822) and −605 HU (−646 to −564) respectively, with a mean Δ-HU density (95%CI) of 229 HU (188 to 269) (Fig. 4). A significant difference (95%CI) was demonstrated between the two cohorts for both inspiratory [41 HU (28 to 54) ($p < 0.0001$)] and expiratory [166 HU (118 to 215) ($p < 0.0001$)] sequences. The mean Δ-HU density (95%CI) was 207 HU (159 to 256) higher in the COP group compared with GOT group ($p < 0.0001$). Inspiratory-expiratory change in HU density (Δ-HU density) did not correlate with age or lung function parameters. We investigated the influence of slice thickness on HU density measurements by comparing data generated from 3 vs. 1 mm reconstruction slices from the same patients at the COP centre. We found a correlation coefficient of 0.98 between 3 vs. 1 mm slice thickness for HU measurements, confirming that reconstruction slice thickness had minimal to no impact on lung density measurements (A plot of the 1 to 3 mm correlation is available online).

3.2. CT evaluation

TA was classified dichotomously in 40 subjects, and the observers agreed for 38/40 (95%) of the double scored scans

Table 1
Characteristics of CF children from Copenhagen and Gothenburg.

	Copenhagen n = 42 (22 males (52.4%))			Gothenburg n = 37 (21 males (56,8%)			p
	Mean (95% CI)	min	max	Mean (95% CI)	min	max	
Age	11.2 (10.2–12.2)	6.4	17.1	11.0 (10.0–12.1)	6.2	17.8	NS
BMI	17.0 (16.3–17.8)	13.3	25.3	17.4 (16.7–18.1)	13.7	23.0	NS
FEV_1 (% pred)	96.9 (93.4–100.5)	69.0	119.1	98.0 (93.4–102.5)	57.8	127.2	NS
FVC (% pred)	102.9 (99.1–106.6)	75.6	134.4	102.5 (99.0–106.0)	73.0	125.9	NS
FEV_1/FVC (%)	94.5 (92.0–97.0)	71.0	106.9	95.7 (93.0–98.4)	65.0	114.1	NS

(35 abnormal and 3 normal; κ = 0.72). When assessing the total TA score, there was a good ICC between observers (ICC = 0.76) for the 40 subjects evaluated.

The subsequent mean TA score (95%CI) for all subjects demonstrated a significantly higher TA score in the COP cohort (6.93 (6.05 to 7.82)) compared to the GOT cohort (3.81 (2.89 to 4.73)) ($p < 0.0001$) (Fig. 5). TA scores were significantly correlated with Δ-HU density ($R = 0.60$ $p < 0.0001$) (Fig. 6) and age ($R = 0.24$ $p = 0.031$). Adjustment of TA-score according to the Δ-HU density using multiple regression analysis changed the difference in TA score between cohorts from significant to non-significant ($p = 0.29$) findings. There was no significant difference between the cohorts in any of the inspiratory CFCT scoring parameters including the total CFCT score (Table 2).

4. Discussion

This study demonstrated that an monitored breath hold control manoeuvre results in a larger change in lung density measurements between inspiratory and expiratory imaging, and a higher TA score compared with the unmonitored breath hold technique in CF children with comparable disease severity.

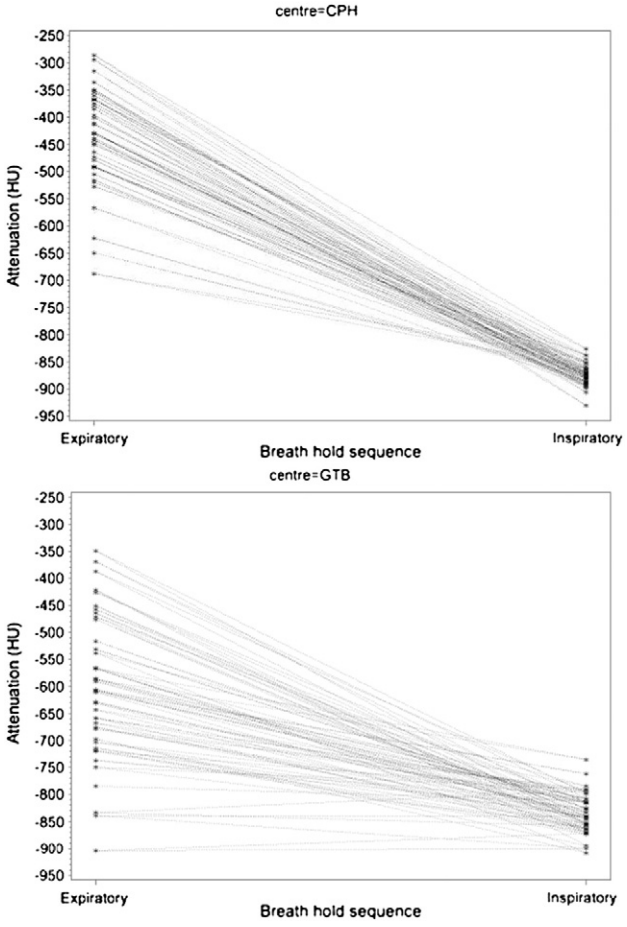

Fig. 4. Lung attenuation during inspiratory and expiratory sequences for the Copenhagen A) and Gothenburg B) group. A successful breath hold manoeuvre provides a large change in attenuation between sequences.

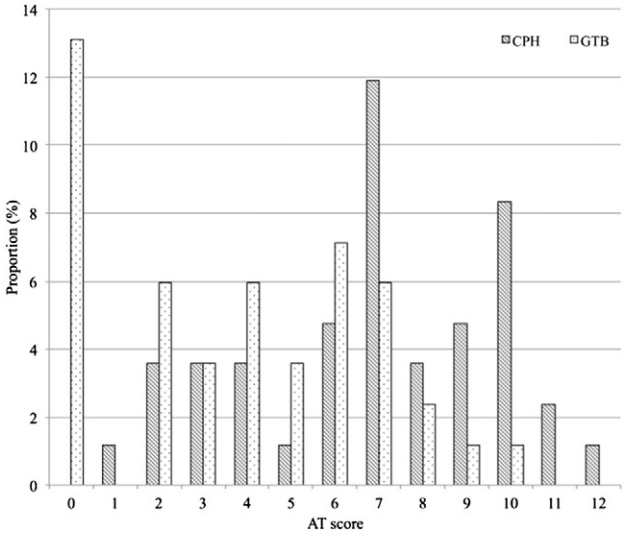

Fig. 5. Air trapping scores in the Copenhagen (CPH) and Gothenburg (GTB) centre. A maximum score of 12 is given if air trapping is seen in more than 50% of lung tissue in all 3 expiratory images. The GTB group scores are significantly lower than the CPH group ($p < 0.0001$).

4.1. Air trapping

Air trapping is an important early marker of lung disease in young children with CF as demonstrated by Mott et al. [6]. Air trapping is also important in older CF children, who despite normal lung function, often exhibit underlying structural CF

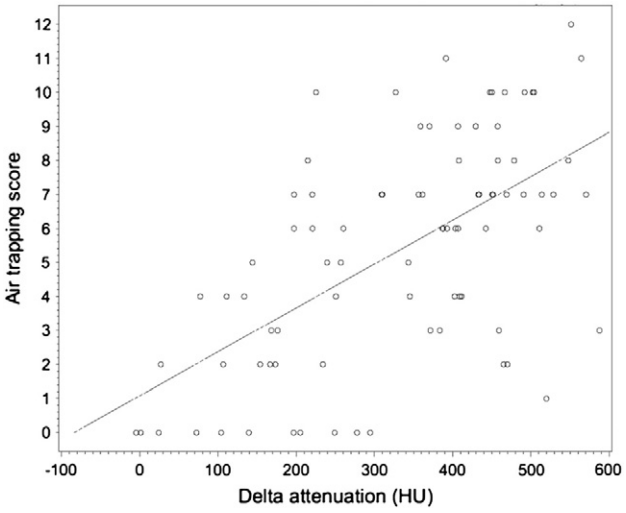

Fig. 6. Scatter plot showing the correlation between air trapping score and delta attenuation. ($R = 0.57$ $p < 0.0001$) An ineffective breath hold manoeuvre with a small change in lung attenuation is more likely to result in a low air trapping score.

Table 2
CFCT score in % of maximal score.

	Copenhagen mean (95%CI)	SD	Gothenburg mean (95%CI)	SD	p
Bronchiectasis	6.7 (3.9–11.2)	11.7	10.7 (6.8–14.5)	12.4	NS
Airway Wall Thickening	8.2 (5.6–10.7)	8.2	10.2 (6.5–13.9)	11.9	NS
Mucus plugging	3.4 (1.2–5.5)	6.8	4.6 (2.0–7.2)	8.3	NS
Parenchyma	1.5 (0.8–2.2)	2.1	2.2 (1.3–3.2)	3.1	NS
Total score	5.5 (3.4–7.6)	6.7	7.4 (4.9–10.0)	8.2	NS

lung disease. Application of an optimal sensitive technique for detecting air trapping is therefore of great importance. Spirometric monitored CT provides lung images that clearly discriminate TA on expiratory scans compared to those acquired without breath hold control, which is highlighted by the significant difference in TA scores. Thus, it will likely improve the value of CT examinations, not only for the physician monitoring disease progression in CF children, but also for the use of TA as an outcome parameter in clinical trials, since this parameter is clearly dependent upon a standardized chest CT breath hold technique.

The difference observed in the TA score between the two cohorts in our study is not likely explained by less peripheral airway disease in GOT patients compared to COP patients. The cohorts had closely matched lung function parameters (Table 1) and we assume that the difference was a result of the improved breath hold manoeuvre, since TA significantly correlates with lung function parameters [29,30]. The lack of significant difference found when adjusting for Δ-HU density by multiple regression analysis, and the small insignificant differences in the CFCT scoring parameters, supports these assumptions.

Goris et al. utilized a comparable breath holding technique to the method described in this paper [11]. The results of lung density measures from that study demonstrated a smaller difference in respect to inspiratory–expiratory Δ-HU density measurements compared to our results. These differences are likely due to the more simplified method used in our study to measure lung density from region of interest on limited slices compared to sampling of the entire segmented lung, as utilized by Goris et al. Despite these differences, their technique similar to ours provided greater discrimination of air trapping.

In this study we describe a real-time feedback animation, resembling the incentive used in cold air challenge of young children [31]. The incentive optimizes full inflation and deflation CT scans utilizing spirometric techniques. We did not investigate, however, the effect of the animation software in itself, and in the hands of an experienced lung function technician, similar quality results might be achieved without it. During this study we found that many children followed the feedback animation and found it helpful; others did not. This was not investigated further.

During CT scanning the instructor was standing next to the child and was thus exposed to a certain low amount of radiation. Even though this was addressed by wearing a lead apron, and a thyroid shield, it could be avoided altogether by using extension wires to the portable spirometry unit, allowing for distant monitoring and instruction of the patient from the CT console room.

4.2. Limitations

In this study TA was reviewed on only 3 expiratory slices, which was the standard protocol used in GOT. This could underestimate the degree of TA, and thus impose a methodological error [32,33]. The slice thickness was also different in the two cohorts which could underestimate the degree of TA in the GOT cohort. Another limitation in this study includes the use of different CT scanners utilizing different CT protocols and reconstruction algorithms for each centre, which made it difficult to completely conceal the affiliation of the chest CT images. In spite of selecting images with comparable noise/signal ratios, blinding of observers was therefore not optimal and could have created some observer bias in the evaluation of images. Furthermore, the different scanners at the two centres may likely have imparted some differences in the results of lung density measurements. Birnbaum et al. [26] have shown that there are differences in attenuation between CT scanners, but these differences are small and indeed accounted for in this study, as Δ-HU density (inspiratory–expiratory) on the same scanner is used for comparison.

In general, comparing different cohorts of children with CF can be difficult and inappropriate due to differences in treatment regimes and patient demographics. However, the centres involved in this study share many guidelines in treatment of CF and the closely overlapping lung function parameters and CFCT score parameters in the cohorts make comparison of the cohorts reasonable. The ideal study design would include a cohort of CF children utilizing the two techniques (real-time spirometric monitoring vs. un-monitored breath hold manoeuvres) for chest CT scanning on the same CT scanner. Less optimal would be a comparison of two cohorts from the same centre using the two breath hold techniques. However, these approaches would not be feasible given the increase in radiation exposure risk with two chest CT scans without any direct benefit to the child.

Due to lack of eligible patients in some age groups, the CT scans from 5 patients in the GOT centre who had two examinations at different ages were included (time span 3 to 6 years). A recalculation of the statistical analysis, only including one examination per child and excluding all non-matched individuals, produced similar significant results.

4.3. Conclusion

Advanced spirometric breath hold monitoring during CT examination of children is a feasible method of optimizing image usefulness in CF lung disease evaluation and monitoring. As we hypothesized, the changes in lung density between inspiratory and expiratory sequences are significantly greater than with unmonitored breath hold manoeuvres, and TA scores become more reliable and comparable. A standard

JAEGER pneumotachograph was used, and no alterations to CT scanners or other equipment were necessary, which makes it feasible to introduce this technique at most CF centres. The authors therefore highly recommend that spirometric breath hold monitoring is used in both clinical practice and research projects.

Ethical approval

The study was approved by the regional ethics committee, Capital Region of Denmark (Protocol no: H-1-2010-042) and the regional ethics committee in GOT, Sweden (quality assurance).

Conflicts of interests

None of the authors have any conflicts of interest relevant to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcf.2013.05.012.

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